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# Severe Acute Respiratory Syndrome (SARS): A Review of the History, Epidemiology, Prevention, and Concerns for the Future

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**During the first part of 2003, the world experienced the first epidemic of the 21st century with the emergence of a new and readily transmissible disease. The disease, severe acute respiratory syndrome (SARS), spread quickly and caused numerous deaths, as well as public panic. This article provides a brief review of the initial history of the epidemiology, as well as of the clinical definition, occurrence in the pediatric population, etiology, prevention, drug studies, and considerations for the future.**  
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On November 16, 2002, the first severe and readily transmissible new disease to emerge in the 21st century, severe acute respiratory syndrome (SARS), began in Guangdong Province, China and spread rapidly.<sup>1,2</sup> By June 26, 2003, 7 months later, the World Health Organization (WHO) showed reports from 33 countries totaling 8456 cumulative cases and 809 deaths.<sup>3</sup> Earlier in that same week, WHO removed Hong Kong and Beijing, the two most severely affected cities, from the list of areas having recent local transmission of SARS; only Toronto and Taiwan continued to report instances of local transmission. This article provides a brief review of the history of the spread of the disease, as well as of the clinical definition, occurrence in the pediatric population, etiology, prevention, drug studies, and considerations for the future. For more detailed information, the reader should consult the WHO website (<http://www.who.int/csr/sars/en/>), the website of the Centers for Disease Control and Prevention (CDC) (<http://www.cdc.gov/ncidod/sars/index.htm>), the cumulative SARS reference text accessible on the Internet (<http://sarsreference.com>), and the articles referenced herein.

## History: The Emergence and Rapid Spread of a New Disease

The first report of the new disease, given the name "severe acute respiratory syndrome" (SARS), was received by WHO on February 11 from the Chinese Ministry of Health, which documented that 305 cases and 5 deaths had occurred in the Guangdong Province.<sup>2</sup>

### Hong Kong

Two days later, on February 21, a 65-year-old physician who had treated patients for what was thought to be atypical pneumonia checked into a 4-star hotel in Hong Kong and was given a room on the 9th floor.<sup>2</sup> He had begun having symptoms five days earlier, but upon arrival in Hong Kong, he felt well enough to go sightseeing and shopping with his brother-in-law. However, the next day, he sought urgent care and was admitted with respiratory failure to the intensive care unit of a hospital.<sup>4</sup> He unwittingly had transmitted the disease to at least 12 other guests and visitors to the 9th floor, with the result that the disease was spread quickly worldwide.<sup>2</sup> On March 4, an individual who earlier had visited the 9th floor of the Hong Kong hotel was admitted to the Prince of Wales Hospital in Hong Kong with respiratory symptoms for which he was treated for 7 days with a jet nebulizer four times a day.<sup>2</sup>

### Vietnam

One of the guests at the same hotel, a 48-year-old Chinese-American businessman, became ill with high fever, dry cough, myalgia, and mild sore throat and was admitted on February 26 to the French Hospital in Hanoi. He later was evacuated to Hong Kong, where he died. Two days later, Dr. Carlo Urbani, a WHO official in Vietnam, reported an alarming number of patients being treated at the French Hospital for atypical pneumonia.<sup>2,5</sup> By March 5, secondary probable SARS cases were identified among healthcare workers in Hanoi, and at the urging of Dr. Urbani and his colleagues, Vietnam closed the hospital to new patients and visitors on March 11. Most of the hospital's staff remained in the hospital; some of them fell ill while others watched their colleagues sicken and die. Prompt action taken by a steering committee led by the health minister was instrumental in containing the disease. By May 7, the Hanoi French Hospital had transferred the last of its patients to another hospital and was being thoroughly disinfected.<sup>6</sup>

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### Singapore

Another hotel guest staying on the 9th floor proved to be the index case of SARS in Singapore. A previously healthy 23-year-old woman of Chinese ethnicity, she had been on a vacation to Hong Kong from February 20 to February 25. She developed fever and a headache on February 25 and a dry cough on February 28. On March 1, she was admitted to a hospital in Singapore, where over the course of several days, she infected at least 20 other people. No further transmission from this patient was observed after strict infection control measures (use of N95 masks, gown, gloves, and handwashing before and after patient contact) were implemented.<sup>5,7</sup> As of May 5, 204 cases of SARS had been diagnosed in Singapore and 26 patients had died.<sup>5</sup>

### Toronto

On March 5, yet another guest on the 9th floor of the hotel, a 78-year-old Toronto woman, died from SARS; subsequently member of her family were admitted to the hospital.<sup>2,5,8</sup> The patient and her husband had traveled to Hong Kong from February 13 to February 23 to visit relatives. Two days after returning home, the woman, who had a history of type 2 diabetes and coronary heart disease, developed fever, anorexia, myalgia, a sore throat, and mild nonproductive cough. Three days later, her doctor examined her and found pharyngeal erythema but no other abnormalities; she was prescribed an oral antibiotic and was sent home. Two days later, she noticed the development of increasing cough with dyspnea, and on March 5, 9 days after the onset of her illness, she died at home.<sup>8</sup>

### Taiwan

Soon, cases of SARS were occurring in Taiwan. The first 2 suspected cases were diagnosed in a couple on March 14. The man had traveled in February to the Guangdong Province and to Hong Kong. On March 26, a Taiwanese resident of Hong Kong's Amoy Gardens flew to Taiwan and took a train to Taichung to celebrate the traditional festival Qing Ming. His brother became Taiwan's first SARS fatality. A fellow passenger on the train also was affected. The number of cases began to increase steadily during the last weeks of April. On April 28, the Taiwanese government imposed a mandatory 14-day quarantine on all incoming travelers from China, Hong Kong, Singapore, Macau, and Toronto. As of May 5, 2003, 116 cases of SARS had been diagnosed in Taiwan, and 8 patients had died.<sup>5</sup>

By the time the cases occurred in Taiwan, reports had begun flooding into WHO from different parts of the world. On March 8, 14 staff members of the private French Hospital in Hanoi were ill with an acute respiratory syndrome, and a WHO team arrived to provide support. By March 11, at least 20 hospital personnel in the Hanoi hospital and 23 at the Prince of Wales Hospital in Hong Kong were ill with an unidentified acute respiratory syndrome.<sup>2,9</sup>

On March 12, WHO issued a global alert concerning the spread of a severe atypical pneumonia with unknown etiol-

**Table 1.** Factors Leading to the Global Alert Issued by WHO on March 15, 2003<sup>2</sup>

1. The causative agent and the potential for spread were still unknown.
2. The outbreaks appeared to pose a great risk to health care workers, family members, and other close contacts of patients.
3. None of the different antibiotics and antivirals that had been tried empirically seemed to have an effect.
4. Although the numbers still were relatively small, the clinical course had progressed rapidly to respiratory failure, requiring intensive care, and many previously healthy patients had died.
5. The disease had spread from its initial focus in Asia to North America and Europe.

ogy. Three days later, with more instances of the disease being reported, WHO decided on the basis of 5 factors (Table 1) to increase the level of the global alert issued on March 12.<sup>2</sup>

### SARS Definition

Several criteria, namely clinical, epidemiologic, and laboratory, have been established by the CDC as criteria for the definition of SARS (Table 2). A "probable" case is defined as one that "meets the clinical criteria for severe respiratory illness of unknown etiology and epidemiologic criteria for exposure; laboratory criteria confirmed, negative, or undetermined." A "suspect" case is that "meets the clinical criteria for moderate respiratory illness of unknown etiology, and epidemiologic criteria for exposure; laboratory criteria confirmed, negative, or undetermined." A case can be excluded as being either suspect or probable if an alternative diagnosis can fully explain the illness or the case was reported on the basis of contact with a suspected index case that subsequently was excluded as a case of SARS, provided other possible epidemiologic exposure criteria are not present.<sup>10</sup>

### SARS in Children

SARS appears to take a less aggressive clinical course in younger children in comparison to that seen in adults and teenagers.<sup>11</sup> Until April 25, children younger than 15 years of age, accounted for only 3 percent of all cases reported in Hong Kong. The reason for this low percentage is unclear.<sup>5</sup>

The first publication on SARS in the pediatric population comes from Hon and colleagues. Because most data available were on adults, they decided to report on their experience in treating children at the Prince of Wales and Princess Margaret hospitals in Hong Kong. Between March 13 and 28, 2003, they admitted 10 children with suspected cases of SARS. All 10 children satisfied the WHO case definition for SARS, had been in close contact with infected adults, and had fever that lasted for a median duration of 6

**Table 2.** Centers for Disease Control and Prevention Case Definition of SARS<sup>10</sup>**Clinical Criteria**

- Asymptomatic or mild respiratory illness
- Moderate respiratory illness
  - Temperature of  $>100.4^{\circ}\text{F}(>38^{\circ}\text{C})^{*}$ , and
  - One or more clinical findings of respiratory illness (eg, cough, shortness of breath, difficulty breathing, or hypoxia).
- Severe respiratory illness
  - Temperature of  $>100.4^{\circ}\text{F}(>38^{\circ}\text{C})^{*}$ , and
  - One or more clinical findings of respiratory illness (eg, cough, shortness of breath, difficulty breathing, or hypoxia), and
  - radiographic evidence of pneumonia, or
  - respiratory distress syndrome, or
  - autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause.

**Epidemiologic Criteria**

- Travel (including transit in an airport) within 10 days of onset of symptoms to an area with current or previously documented or suspected community transmission of SARS (see Table), or
- Close contact within 10 days of onset of symptoms with a person known or suspected to have SARS

**Laboratory Criteria**

- Confirmed
  - Detection of antibody to SARS-CoV in specimens obtained during acute illness or  $>21$  days after illness onset, or
  - Detection of SARS-CoV RNA by RT-PCR confirmed by a second PCR assay, by using a second aliquot of the specimen and a different set of PCR primers, or
  - Isolation of SARS-CoV.
- Negative
  - Absence of antibody to SARS-CoV in convalescent serum obtained  $>21$  days after symptom onset.
- Undetermined
  - Laboratory testing either not performed or incomplete.

days. The authors noted 2 distinct patterns of clinical presentation: teenage patients presented with symptoms of malaise, myalgia, chill, and rigor similar to those of adults, whereas the younger children presented primarily with cough and runny nose; none had chills, rigor, or myalgia. The younger children also experienced much shorter and milder clinical courses, and radiological changes were milder and generally resolved more quickly than in the teenagers. Although all of the patients had clinically important lymphopenia, the teenagers suffered more severe cases. All patients were treated with a regimen of ribavirin and steroids similar to that used in adults SARS patients. A detailed table listing the ages, sex, clinical features, laboratory findings, radiological findings, and treatment and outcome is available in the article, which also can be accessed at <http://image.thelancet.com/extras/03let4127web.pdf>.

## Prevention: WHO Efforts to Stop Further Spread of SARS

Using the Global Outbreak Alert and Response Network (GOARN), a WHO mechanism launched in 2000 to link together 112 existing networks with extensive data resources, expertise, and skills, WHO initiated an emergency plan that called for 2 arenas of attack, 1 on land and 1 in the air. The land initiative involved sending teams of experts and specialized protective equipment for infection control to countries requesting such assistance. The land attack involved establishing a “virtual” network of 11 leading laboratories connected by a shared secure website and daily teleconferences; this network worked around the clock to identify the causative agent of SARS and to develop a robust and reliable diagnostic test. The results from the establishment of the laboratory network were the conclusive identification of the causative agent of SARS only a month later and the complete sequencing of its RNA shortly thereafter (see below).<sup>2</sup>

## Etiology

Immediately after the incidence of SARS was recognized, researchers were at work attempting to identify the etiological agent. Shortly thereafter, perhaps at record speed, the culprit was identified. On April 10, 2003, the first publications, initially published on-line, reported the identification of a novel coronavirus.

Drosten and colleagues<sup>12</sup> reported that they had isolated “a novel coronavirus” in cell culture and had obtained a sequence 300 nucleotides in length using polymerase chain reaction (PCR)-based random amplification. On the basis of the obtained sequence, they established conventional and real-time PCR assays for specific and sensitive detection of the novel virus; the assays detected a variety of clinical specimens from patients with SARS but not from controls. High concentrations (up to 100 million molecules per milliliter) were found in sputum, and viral RNA also was detected at extremely low concentrations in plasma during the acute phase and in faces during the late convalescent phase. The authors suggested that the novel coronavirus might have a role in causing SARS.

The other report came from Ksiazek and associates,<sup>13</sup> who reported that no classic respiratory or bacterial respiratory pathogen was identified consistently, but that a novel coronavirus was isolated from patients who met the case definition of SARS. Cytopathic features were noted microscopically in Vero E6 cells that had been inoculated with a throat-swab specimen. Electron microscopic examination revealed ultrastructural features characteristic of coronaviruses. Reactivity with group I coronavirus polyclonal antibodies was revealed using immunohistochemical and immunofluorescence staining. The authors used consensus coronavirus primers designed to amplify a fragment of the polymerase gene by reverse transcription-polymerase chain reaction (RT-PCR) to obtain a sequence that clearly identified the isolate as a unique coronavirus only distantly

**Table 3.** Lessons Learned from the SARS Outbreak

<i>Lesson</i>	<i>Means</i>
The capacity of global alerts to improve awareness and vigilance	Wide support by responsible press and amplified by electronic communications
The advantage of quick detection and reporting	Immediate reporting of initial cases by South Africa and India
The successful containment that can be achieved by readying health services with preparedness plans and campaigns to guard against imported cases	Climate of high alert that was established after reports of the disease became known
The value of immediate political commitment at the highest level	The experience in Vietnam, where the government took immediate measures to protect its people
The ability of even developing countries to triumph over a disease when reporting is prompt and open and when rapid case detection, immediate isolation and infection control, and vigorous contact tracing are put in place.	The appeal by Vietnam, where WHO assistance was requested quickly and fully supported

related to coronaviruses previously sequenced. Using specific diagnostic RT-PCR primers, they were able to identify several identical nucleotide sequences in 12 patients from several locations. Indirect fluorescent antibody tests and enzyme-linked immunosorbent assays made with the new coronavirus isolate demonstrated a virus-specific serologic response. The authors suggested the name Urbani SARS-associated coronavirus as the nomenclature for this virus in honor of one of the authors on the paper, Dr. Carlo Urbani, who had died during the investigation of the initial SARS epidemic.

### Possible Approach to Development of Drugs

Efforts have been underway at various institutions to assess potential anti-SARS-CoV agents in vitro. Ribavirin has been used clinically in SARS patients, but it seems to lack the in vitro efficacy.<sup>1</sup>

Kanchan and colleagues<sup>14</sup> have suggested the viral main proteinase (M<sup>pro</sup>, also called 3CL<sup>pro</sup>), which controls the activities of the coronavirus replication complex, as an attractive target for therapy. They determined crystal structures for human coronavirus (strain 229E) M<sup>pro</sup> and for an inhibitor complex of porcine coronavirus [transmissible gastroenteritis virus (TGEV)] M<sup>pro</sup> and constructed a homology model for SARS coronavirus (SARS-CoV) M<sup>pro</sup>. They noted that the structures reveal a remarkable degree of conservation of the substrate-binding sites, which is further supported by recombinant SARS-CoV M<sup>pro</sup>-mediated cleavage of a TGEV M<sup>pro</sup> substrate. Molecular modeling suggests that available rhinovirus 3C<sup>pro</sup> inhibitors may be modified to make them useful for treating SARS.

### Warnings, Lessons, and Questions for the Future

This particular epidemic alone has resulted in untold costs beyond the immediate health concerns. By May 2003, the estimated costs in the Far East alone were approximately

\$30 billion. Other concerns involved the worldwide public panic, with its emotional and psychological tolls; the social instability that occurred in the hardest hit areas; the loss of jobs by some government officials; the closures of hospitals, schools, and borders; and even the deployment in Singapore of military forces to assist in contact tracing and enforcement of quarantines.<sup>2</sup> WHO and researchers from various areas have noted the need to consider the potential for future outbreaks and to be prepared to contain them.

### Warnings

WHO warns that SARS presents a particular threat for several reasons, among which are (1) no vaccine has been developed yet and (2) treatment and containment measures require isolation and quarantine. Furthermore, because the virus comes from a family of viruses notorious for their frequent mutations, it has the potential for future outbreaks and poses problems for development of a vaccine. Epidemiology and pathogenesis remain poorly understood, diagnostic tests have important limitations that allow for contagious individuals to slip through safety nets and infect more individuals, and the disease shows a disturbing concentration among previously healthy hospital staff.<sup>2</sup>

### Lessons

WHO also has identified numerous positive lessons that have been learned from the SARS experience so far (Table 3). Lessons of caution for future incidents also have been identified and include the need to impress upon all countries the responsibility for containing the emergence of any new infectious disease, particularly in a "world where all national borders are porous when confronted by a microbial threat."<sup>2</sup> Other studies point to other measures, such as the use of reduction of contact between infectious individuals and others, quarantine standards adopted with regard to contacts of cases, and the rapid hospitalization of patients, as contributors to the success achieved in containing the diseases.<sup>15</sup> Despite the rapid identification of the causative agent of SARS and the containment of the disease, several

**Table 4.** Concerns Identified by WHO as Result of SARS

1. Inadequate surge capacity in hospitals and public health systems
2. Healthcare providers themselves being the victims of the disease
3. Shortage of expert staff to coordinate national and global responses to a rapidly evolving public health emergency
4. In some cases, the need for hasty construction of new facilities; in other cases, hospitals being closed
5. The power of poorly understood infectious diseases to incite widespread public anxiety and fear, social unease, economic losses, and unwarranted discrimination

deficiencies and concerns also have been identified by WHO (Table 4).<sup>2</sup>

Perhaps the most important lesson is the need to recognize that, in a global economy such as exists today, attempts to conceal cases of an infectious disease for fear of social, economic, political, or other consequences are merely stop-gap measures that have dire results: loss of credibility before the international community, negative domestic economic impact, damage to health and economies of other countries, loss of lives, public panic, and the potential for the offending country's own territory to spiral out of control.<sup>2</sup>

### Questions

In addition to the many lessons that have been learned from the SARS epidemic numerous questions remain. Because this new coronavirus is sufficiently transmissible to cause a large epidemic, it requires that good, basic public health measures be in place. Questions remain about the accuracy of case reports, especially because in many instances the data are poor and instances of underdiagnosis and misdiagnosis are almost inevitable during an outbreak of a new disease. Other questions concern the evident heterogeneity in transmission, especially in light of the extreme instances of transmission in which single individuals apparently infected as many as 300 others. Yet another concern is whether global eradication of SARS can be established.<sup>15</sup>

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